REMARKS

Claims 1-9 were pending in this application. Claims 4, 6 and 8 have been canceled without prejudice, claims 1-3, 5, 7 and 9 have been amended and new claims 10-13 have been added to more particularly recite and distinctly claim the methods of the invention. Support for the amended claims can be found in the specification, *inter alia*, at page 3, line 19. The title, abstract, introduction, and summary of the invention have been amended to delete reference to compositions, in accordance with the claims as amended herein. No new matter has been added by these amendments. Upon entry of the amendments made herein, claims 1-3, 5, 7 and 9-13 will be pending in the application.

Entry of the remarks and amendments contained herein is respectfully requested.

CONCLUSION

Applicants respectfully request entry and consideration of the foregoing amendments and remarks. An early allowance is earnestly sought.

Respectfully submitted,

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Enclosures

EXHIBIT A

Attorney Docket No. 6923-106
U.S. Application No. 09/928,872
Marked Up Version of the Specification

IN THE SPECIFICATION

Please amend the specification as follows:

On page 1, line 1, please amend the title to read as follows:

METHODS [AND COMPOSITIONS] FOR THE MODULATION OF ACID-SPHINGOMYELINASE-RELATED APOPTOSIS

On page 1, line 5, please replace the paragraph beginning "The present invention relates," with the following rewritten paragraph:

The present invention relates, first, to methods [and compositions] for the modulation of acid sphingomyelinase (ASM)- related processes, including apoptosis. Such apoptosis can include, but is not limited to, environmental stress-induced apoptosis such as, for example, ionizing radiation and/or chemotherapeutic agent-induced apoptosis. Apoptosis can be characterized by a cellular morphology comprising cellular condensation, nuclear condensation or zeiosis. The present invention further relates to methods for the identification of compounds which modulate (i.e., either increase or decrease) sensitivity to ASM-related processes, including apoptosis.

On page 3, line 14, please replace the paragraph beginning "The present invention relates," with the following rewritten paragraph:

The present invention relates, first, to methods [and compositions] for the modulation of acid sphingomyelinase (ASM)-related processes, including apoptosis. Such apoptosis can include, but is not limited to, environmental stress-induced apoptosis such as, for example, ionizing radiation and/or chemotherapeutic agent-induced apoptosis. Apoptosis can be characterized by a cellular morphology comprising cellular condensation, nuclear condensation or zeiosis.

On page 38, line 2, please replace the paragraph beginning "The present invention relates," with the following rewritten paragraph:

The present invention relates, first, to methods [and compositions] for the modulation of acid sphingomyelinase (ASM)-related processes, including apoptosis. Such apoptosis can include, but is not limited to, environmental stress-induced apoptosis such as, for example, ionizing radiation and/or chemotherapeutic agent-induced apoptosis. Apoptosis can be characterized by a cellular morphology comprising cellular condensation, nuclear condensation or zeiosis. The present invention further relates to methods for the identification of compounds which modulate (i.e., either increase or decrease) sensitivity to ASM-related processes, including apoptosis.

EXHIBIT B

Attorney Docket No. 6923-106
U.S. Application No. 09/928,872
Marked Up Version of the Amended Claims

1. (Amended) A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

(a) contacting an acid sphingomyelinase-deficient cell with a test compound;

(b) exposing the cell to a chemotherapeutic stress stimulus for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity;

(c) exposing an acid sphingomyelinase-deficient cell, in the absence of the test compound, to the chemotherapeutic stress stimulus for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity; and

(d) monitoring the exposed cells of steps (b) and (c) for the presence of an apoptotic morphology,

such that if the cell from step (b) exhibits a more severe apoptotic morphology, than that of the cell from step (c) the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

2. (Amended) A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

(a) contacting an acid sphingomyelinase-deficient cell with a test compound;

(b) exposing the cell to a chemotherapeutic stress stimulus;

(c) exposing an acid sphingomyelinase-deficient cell, in the absence of the test compound, to the chemotherapeutic stress stimulus; and

(d) comparing the levels of sphingomyelin and ceramide present in the exposed cell of step (b) to the levels present in the exposed cell of step (c),

such that if the level of sphingomyelin in the cell of step (b) is less than that of the cell of step (c), or the level of ceramide in the cell of step (b) is greater than that of the cell in step (c), the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

3. (Amended) The method of Claim 1 or 2 wherein the acid sphingomyelinase-deficient cell is part of a genetically engineered nonhuman animal deficient for the acid sphingomyelinase gene.

5. (Amended) A method for identifying a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

(a) contacting a cell exhibiting acid sphingomyelinase activity with a test compound;

(b) exposing the cell to a chemotherapeutic stress stimulus;

(c) exposing a cell exhibiting acid sphingomyelinase activity to the chemotherapeutic stress stimulus, in the absence of the test compound; and

(d) comparing the levels of sphingomyelin and ceramide present in the exposed cell of step (b) to the levels present in the exposed cell of step (c),

such that if the level of sphingomyelin in the cell of step (b) is greater than that of the cell of step (c), or the level of ceramide in the cell of step (b) is less than that of the cell in step (c), the test compound represents a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

7. (Amended) The method of Claim [6] 12 wherein the cell is part of a genetically engineered nonhuman animal deficient in endogenous acid sphingomyelinase gene activity and containing integrated in its cells a functional human acid sphingomyelinase transgene capable of expressing functional human acid sphingomyelinase.

9. (Amended) The method of Claim [4] 1 or 10 wherein the apoptotic morphology comprises cellular condensation, nuclear condensation or meiosis.

EXHIBIT C

Attorney Docket No. 6923-106
U.S. Application No. 09/928,872
Claims as Pending Following Entry of Amendments Made Herein

1. A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

(a) contacting an acid sphingomyelinase-deficient cell with a test compound;

(b) exposing the cell to a chemotherapeutic stress stimulus for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity;

(c) exposing an acid sphingomyelinase-deficient cell, in the absence of the test compound, to the chemotherapeutic stress stimulus for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity; and

(d) monitoring the exposed cells of steps (b) and (c) for the presence of an apoptotic morphology,

such that if the cell from step (b) exhibits a more severe apoptotic morphology, than that of the cell from step (c) the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

2. A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

(a) contacting an acid sphingomyelinase-deficient cell with a test compound;

(b) exposing the cell to a chemotherapeutic stress stimulus;

(c) exposing an acid sphingomyelinase-deficient cell, in the absence of the test compound, to the chemotherapeutic stress stimulus; and

(d) comparing the levels of sphingomyelin and ceramide present in the exposed cell of step (b) to the levels present in the exposed cell of step (c),

such that if the level of sphingomyelin in the cell of step (b) is less than that of the cell of step (c), or the level of ceramide in the cell of step (b) is greater than that of the cell in step (c), the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

3. The method of Claim 1 or 2 wherein the acid sphingomyelinase-deficient cell is part of a genetically engineered nonhuman animal deficient for the acid sphingomyelinase gene.

5. A method for identifying a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

(a) contacting a cell exhibiting acid sphingomyelinase activity with a test compound;

(b) exposing the cell to a chemotherapeutic stress stimulus;

(c) exposing a cell exhibiting acid sphingomyelinase activity to the chemotherapeutic stress stimulus, in the absence of the test compound; and

(d) comparing the levels of sphingomyelin and ceramide present in the exposed cell of step (b) to the levels present in the exposed cell of step (c),

such that if the level of sphingomyelin in the cell of step (b) is greater than that of the cell of step (c), or the level of ceramide in the cell of step (b) is less than that of the cell in step (c), the test compound represents a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

7. The method of Claim 12 wherein the cell is part of a genetically engineered nonhuman animal deficient in endogenous acid sphingomyelinase gene activity and containing integrated in its cells a functional human acid sphingomyelinase transgene capable of expressing functional human acid sphingomyelinase.

9. The method of Claim 1 or 10 wherein the apoptotic morphology comprises cellular condensation, nuclear condensation or meiosis.

10. A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

(a) exposing acid sphingomyelinase-deficient cells, wherein the cells are part of cell lines or a genetically engineered nonhuman animal deficient for the acid sphingomyelinase gene, in the presence or the absence of a test compound, to a chemotherapeutic stress stimulus for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity; and

(b) monitoring the exposed cells of step (a) for the presence of an apoptotic morphology, such that if the cells treated with the test compound exhibit a more severe apoptotic morphology than that of the cells not treated with the test compound, the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

11. A method for identifying a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising:

(a) exposing acid sphingomyelinase-deficient cells, wherein the cells are part of cell lines or a genetically engineered nonhuman animal deficient for the acid sphingomyelinase gene, in the presence or the absence of a test compound, to a chemotherapeutic stress stimulus for a time sufficient to induce apoptosis in a cell exhibiting normal acid sphingomyelinase activity; and

(b) comparing the levels of sphingomyelin and ceramide present in cells treated with test compound to cells untreated with the test compound, such that if the level of sphingomyelin in the cells treated with the test compound is less than that of cells not treated with the test compound, or the level of ceramide in cells treated with the test compound is

greater than in cells not treated with the test compound, the test compound represents a compound which increases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

12. A method for identifying a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising,

(a) exposing transgenic cells, comprised of cells deficient in endogenous acid sphingomyelinase gene activity that contain a functional human acid sphingomyelinase gene capable of expressing functional human acid sphingomyelinase, to a chemotherapeutic stress stimulus in the presence or absence of a test compound; and

(b) comparing the levels of sphingomyelin and ceramide present in cells treated with test compound to cells not treated with the test compound, such that if the level of sphingomyelin in cells treated with the test compound is greater than in cells not treated with the test compound, or the level of ceramide in cells treated with the test compound is less than that of cells not treated with the test compound, the test compound represents a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis.

13. A method for identifying a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis, comprising,

(a) exposing cells, wherein the cells are genetically engineered cells that exhibit a greater level of acid sphingomyelinase activity than non-genetically engineered cells of the same type, to a chemotherapeutic stress stimulus in the presence or absence of a test compound; and

(b) comparing the levels of sphingomyelin and ceramide present in cells treated with the test compound to cells not treated with the test compound, such that if the level of sphingomyelin in cells treated with the test compound is greater than in cells not treated with the test compound, or the level of ceramide in cells treated with the test

compound is less than that of cells not treated with test compound, the test compound represents a compound which decreases a cell's sensitivity to acid sphingomyelinase-related apoptosis.